

Hot Topics in Medicine Webinar Series  
December 7, 2022

# Treating the Chronic Disease of Obesity

## A Review of Current and Future Anti-obesity Medications

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Division of General Internal Medicine  
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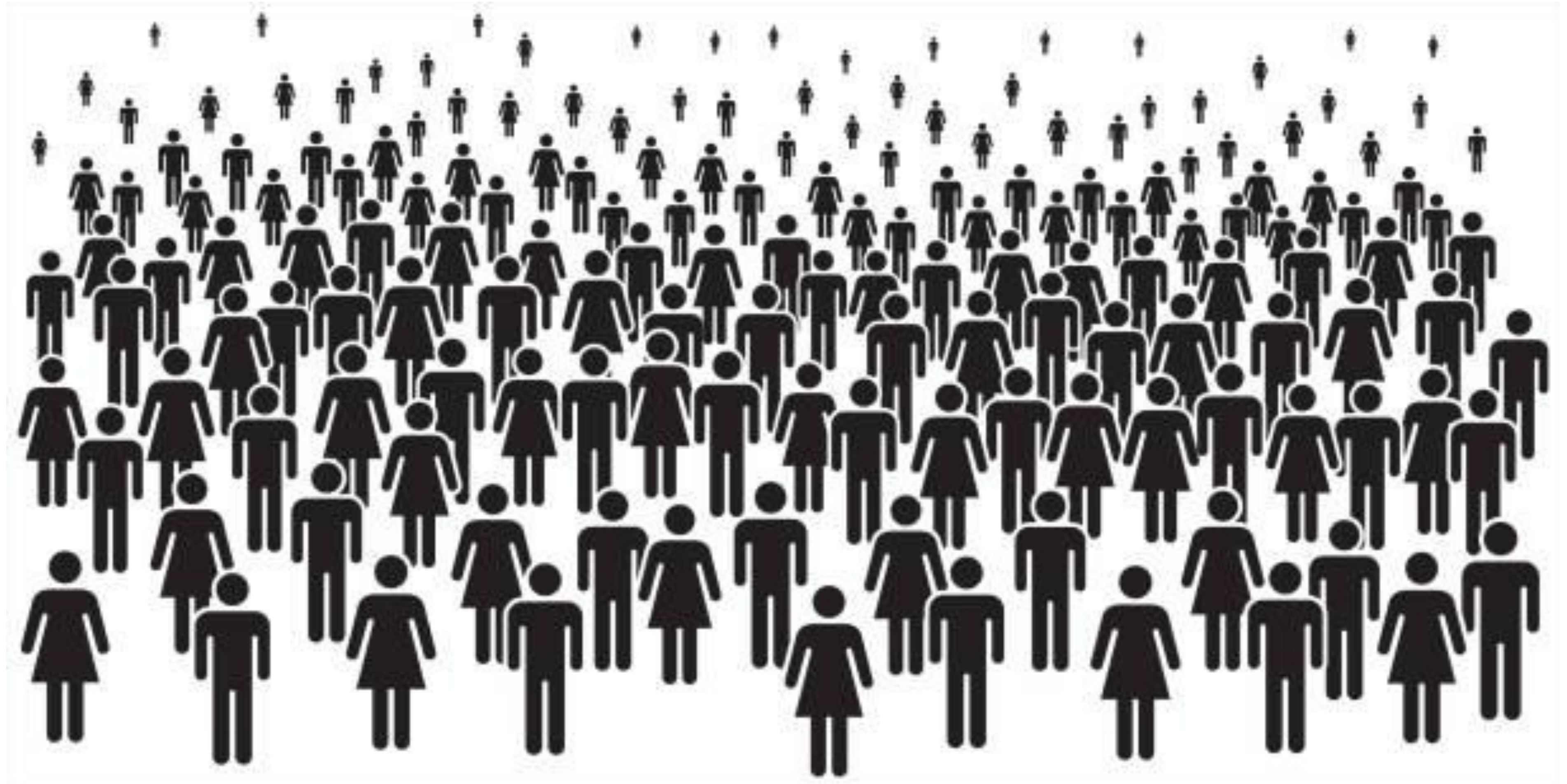
# Relevant Disclosures

Research Support Obesity Treatment Foundation  
Aardvark Therapeutics  
Rhythm Pharmaceuticals  
Eli Lilly

Advisory Board Novo Nordisk (2019 - 2022)  
Currax Pharmaceuticals (2021)  
Gelesis, Inc. (2021)  
B2M Medical (2021 – 2022)

# Overview of Presentation

1. History of anti-obesity therapy
2. Pathophysiology of obesity
3. Current pharmacologic options
4. What's in the pipelines?



# Dark History

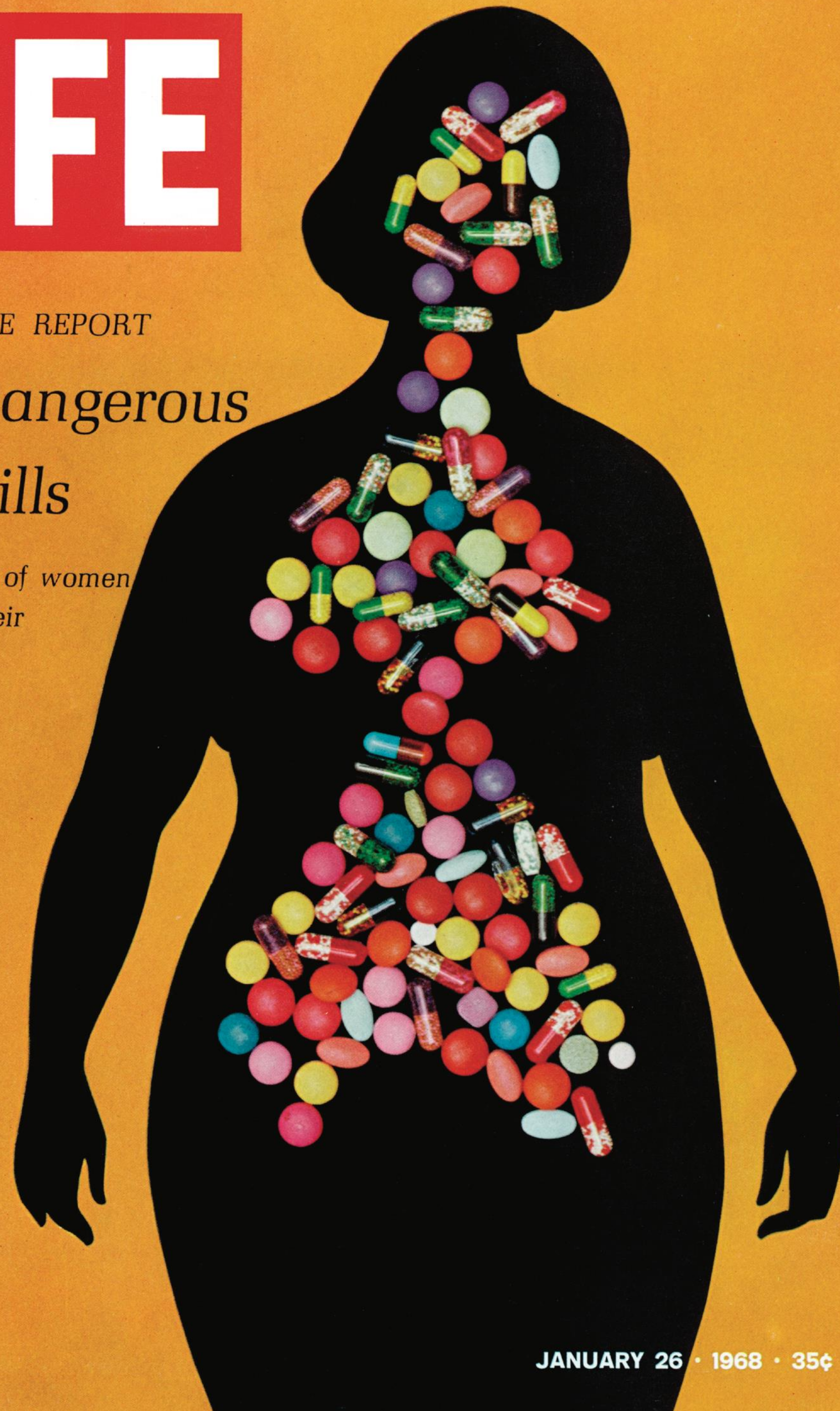


**LIFE**

EXCLUSIVE REPORT

# The Dangerous Diet Pills

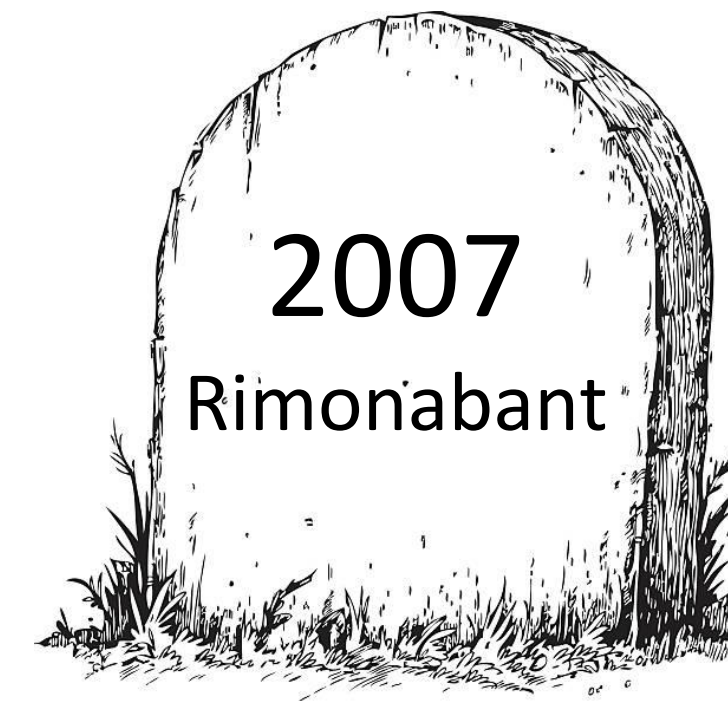
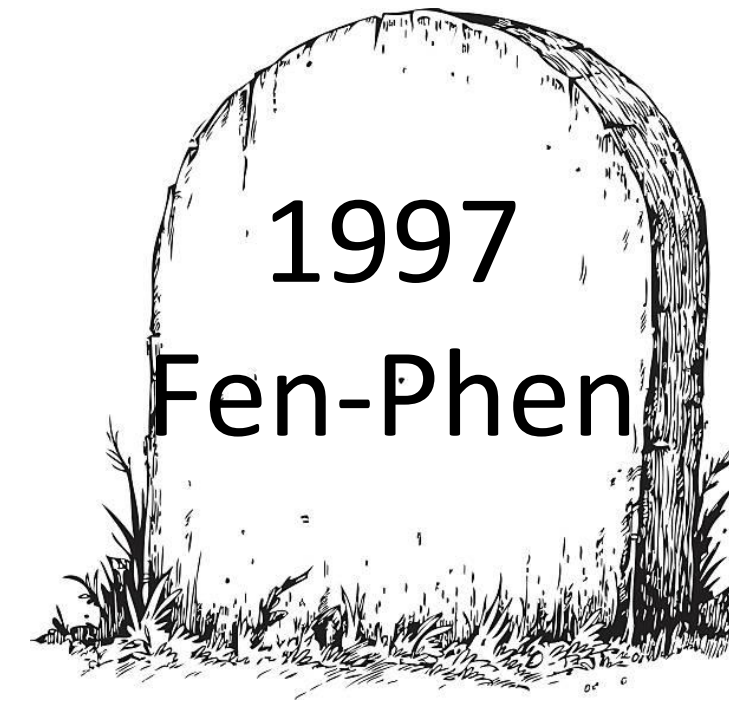
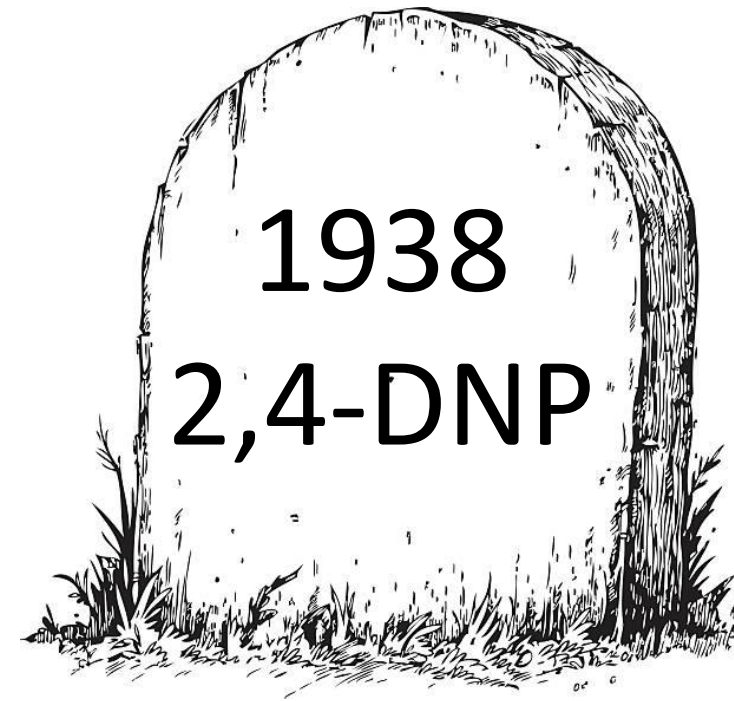
How millions of women  
are risking their  
health with  
'fat doctors'



JANUARY 26 · 1968 · 35¢

UC San Diego  
HEALTH SYSTEM

R.I.P.



# Pharmacotherapy

## Past

Thyroid hormones  
Dinitrophenol  
“Rainbow Pills”  
Fenfluramine  
Dexfenfluramine  
Sibutramine  
Phenylpropanolamine  
Ephedra  
Rimonabant  
HCG  
B12, others  
Lorcaserin

## Present

Orlistat  
Phentermine  
Phendimetrazine  
Diethylpropion  
Benzphetamine  
Phentermine/Topiramate  
Bupropion/Naltrexone  
Liraglutide 3 mg  
Semaglutide 2.4 mg  
Setmelanotide  
Gelesis100

Bupropion\*  
Topiramate\*  
Zonisamide\*  
Metformin\*

Liraglutide 1.8 mg\*\*  
Semaglutide 2.0 mg\*\*  
Dulaglutide\*\*  
Exenatide\*\*  
Canagliflozin\*\*  
Empagliflozin\*\*  
Dapagliflozin\*\*  
Ertugliflozin\*\*  
Pramlintide\*\*

## Future

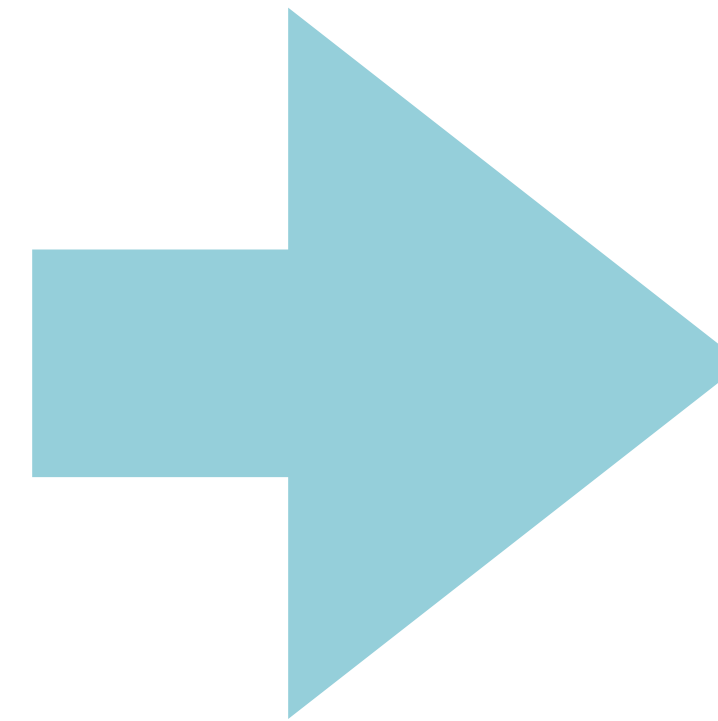
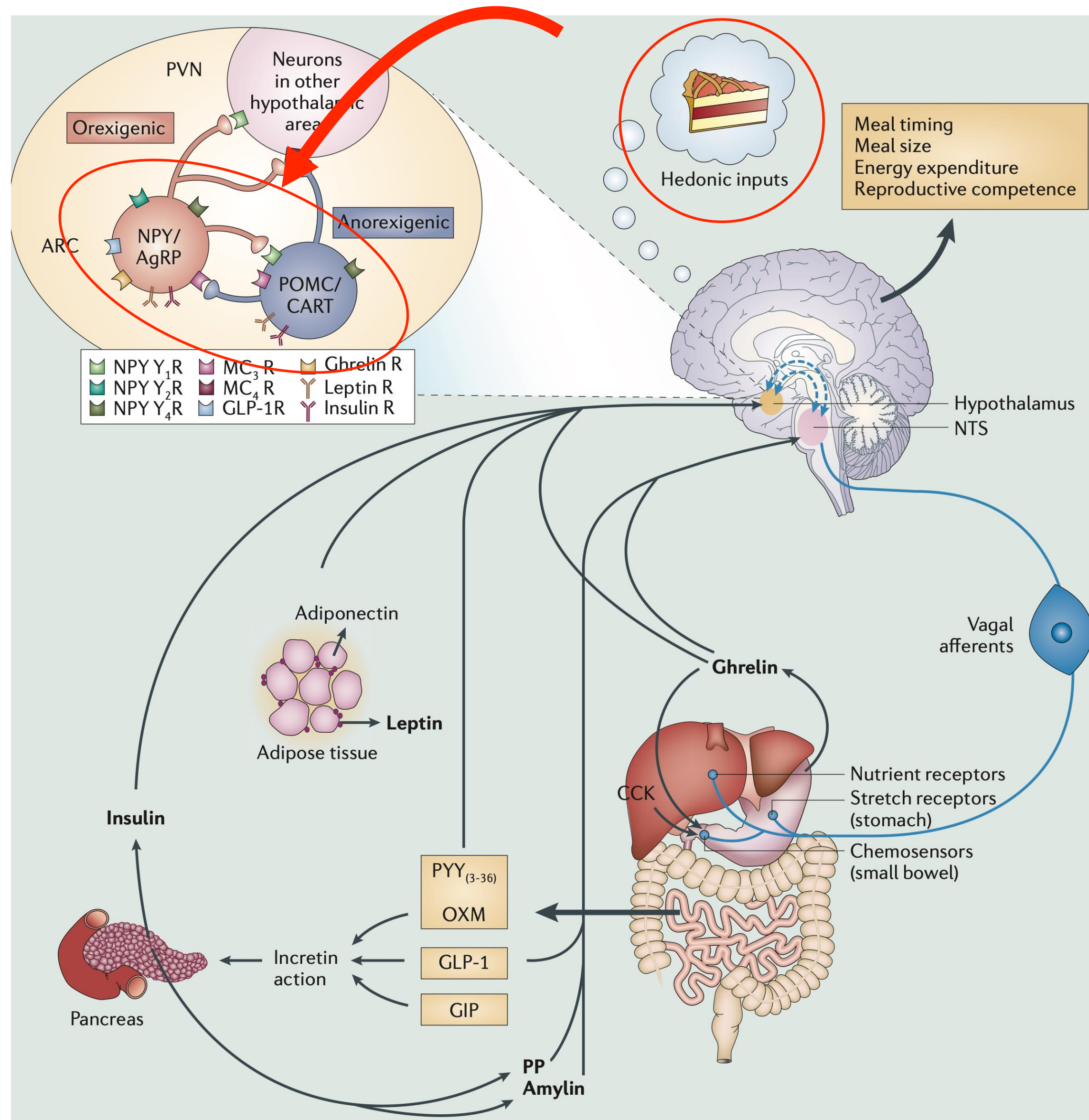
Tirzepatide (GLP1/GIP)  
Pemvidutide  
Cagrilintide  
ZP8396  
Cotadutide  
Oral semaglutide  
Bimagrumab  
AMG133

\*off label

\*\*DM meds

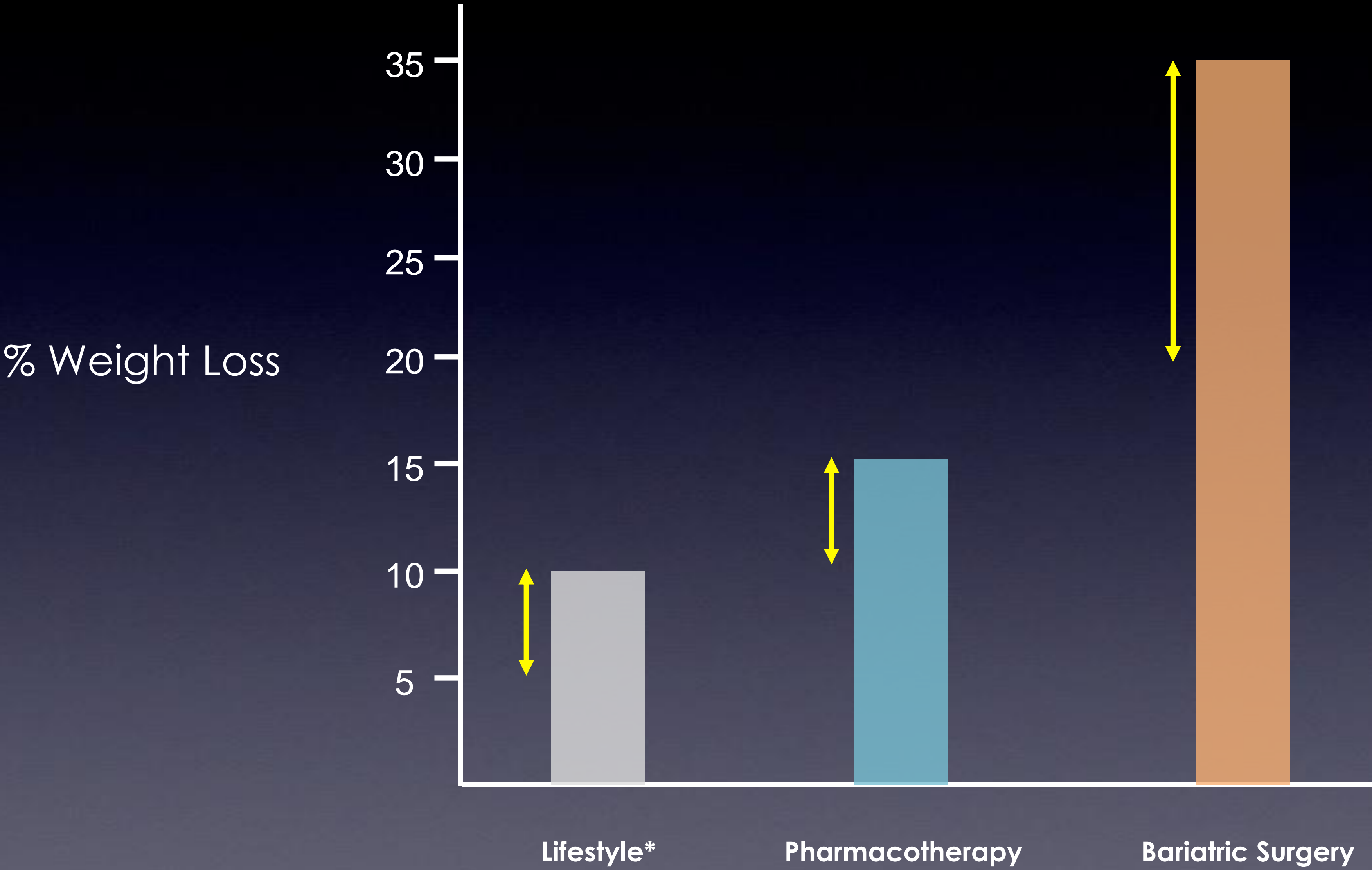


# Integration of Feeding Behavior and Weight Regulation



- ✓ Satiety
- ✓ Satiation
- ✓ Hedonic eating

# Expectations Long-term Weight Loss



\*Lifestyle therapy is always employed with pharmacotherapy and/or bariatric surgery

# Pharmacotherapy: FDA Indications

$\text{BMI} \geq 30 \text{ kg/m}^2$

or

$\text{BMI} \geq 27 \text{ kg/m}^2$  with comorbidities

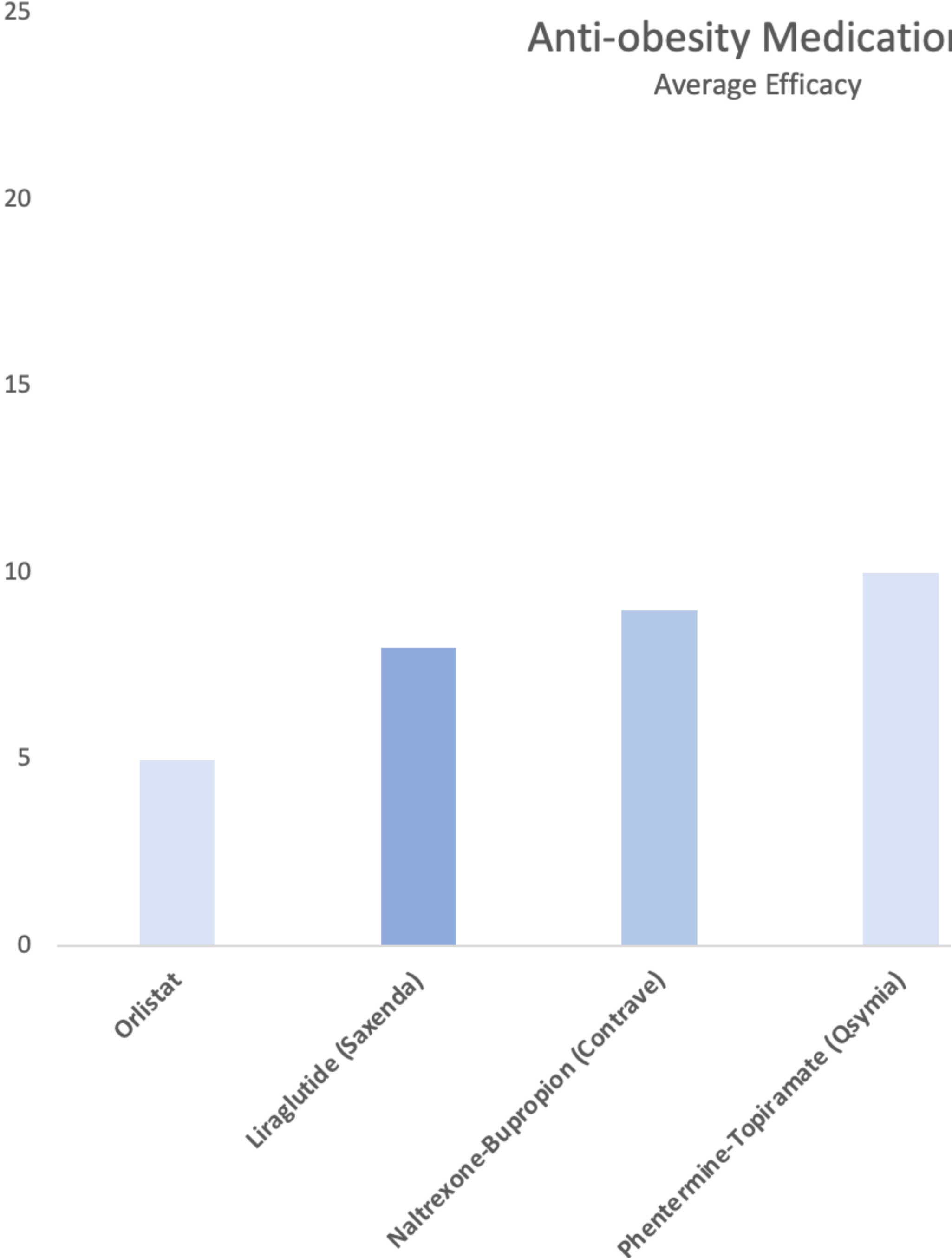
# Pharmacotherapy

Drug	Mechanism of Action	Approval
<b>Phentermine/Topiramate ER</b> <b>(Qsymia™)</b>	<ul style="list-style-type: none"> <li>▶ Norepinephrine reuptake inhibition</li> <li>▶ GABA receptor modulation</li> <li>▶ ? increase metabolic rate</li> </ul>	<b>2012</b>
<b>Bupropion/Naltrexone SR</b> <b>(Contrave™)</b>	<ul style="list-style-type: none"> <li>▶ Dopamine reuptake inhibition</li> <li>▶ Opioid receptor antagonism</li> <li>▶ Enhanced POMC (pro-opiomelanocortin) neuron activation</li> </ul>	<b>2014</b>
<b>Liraglutide 3 mg</b> <b>(Saxenda™)</b>	<ul style="list-style-type: none"> <li>▶ CNS GLP1 (glucagon-like peptide 1) receptor activation</li> <li>▶ Glycemic control</li> <li>▶ Delayed gastric motility</li> </ul>	<b>2015</b>
<b>Semaglutide 2.4 mg</b> <b>(Wegovy™)</b>		<b>2021</b>

# Anti-obesity Medications

Average Efficacy

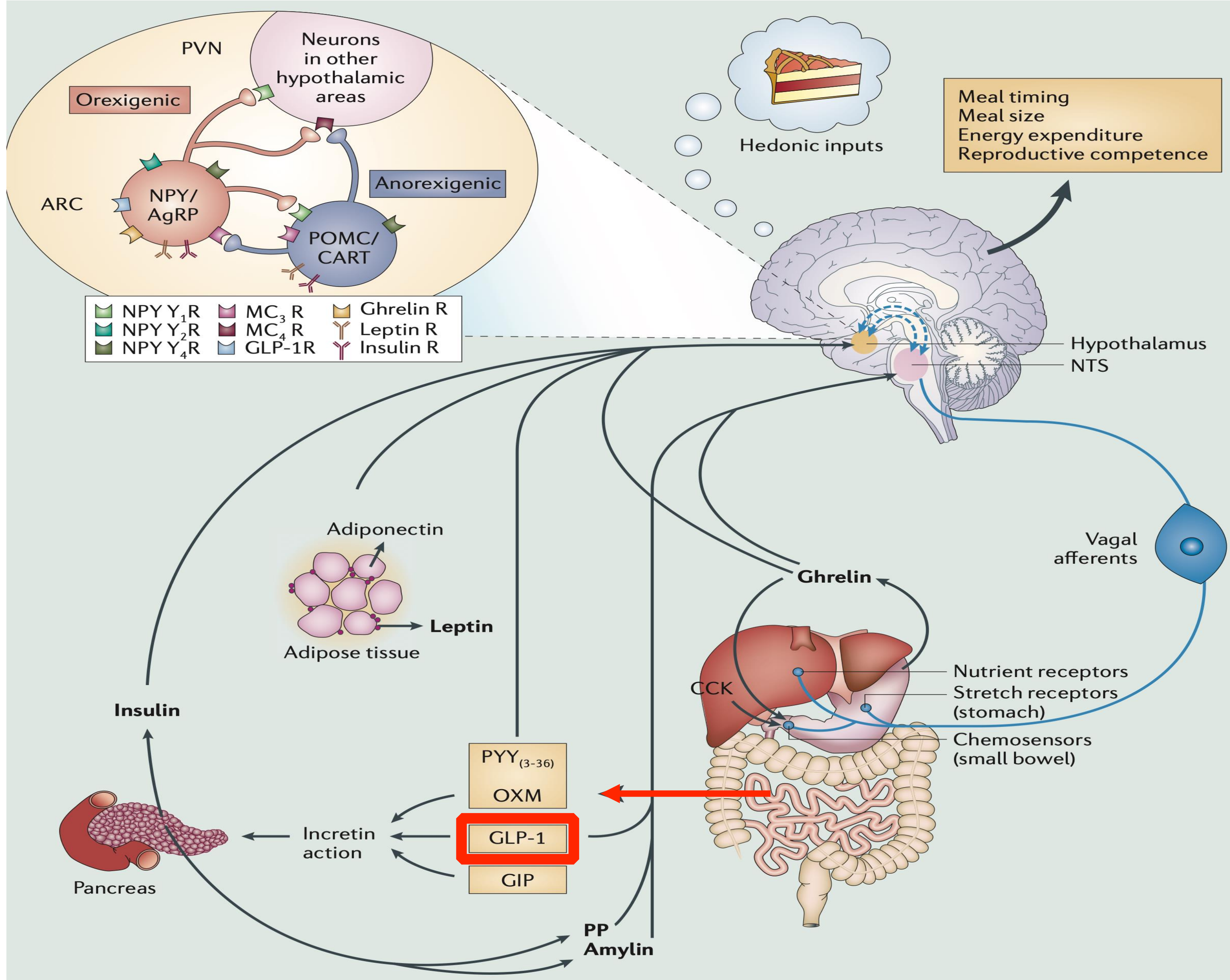
% weight loss



# GLP-1

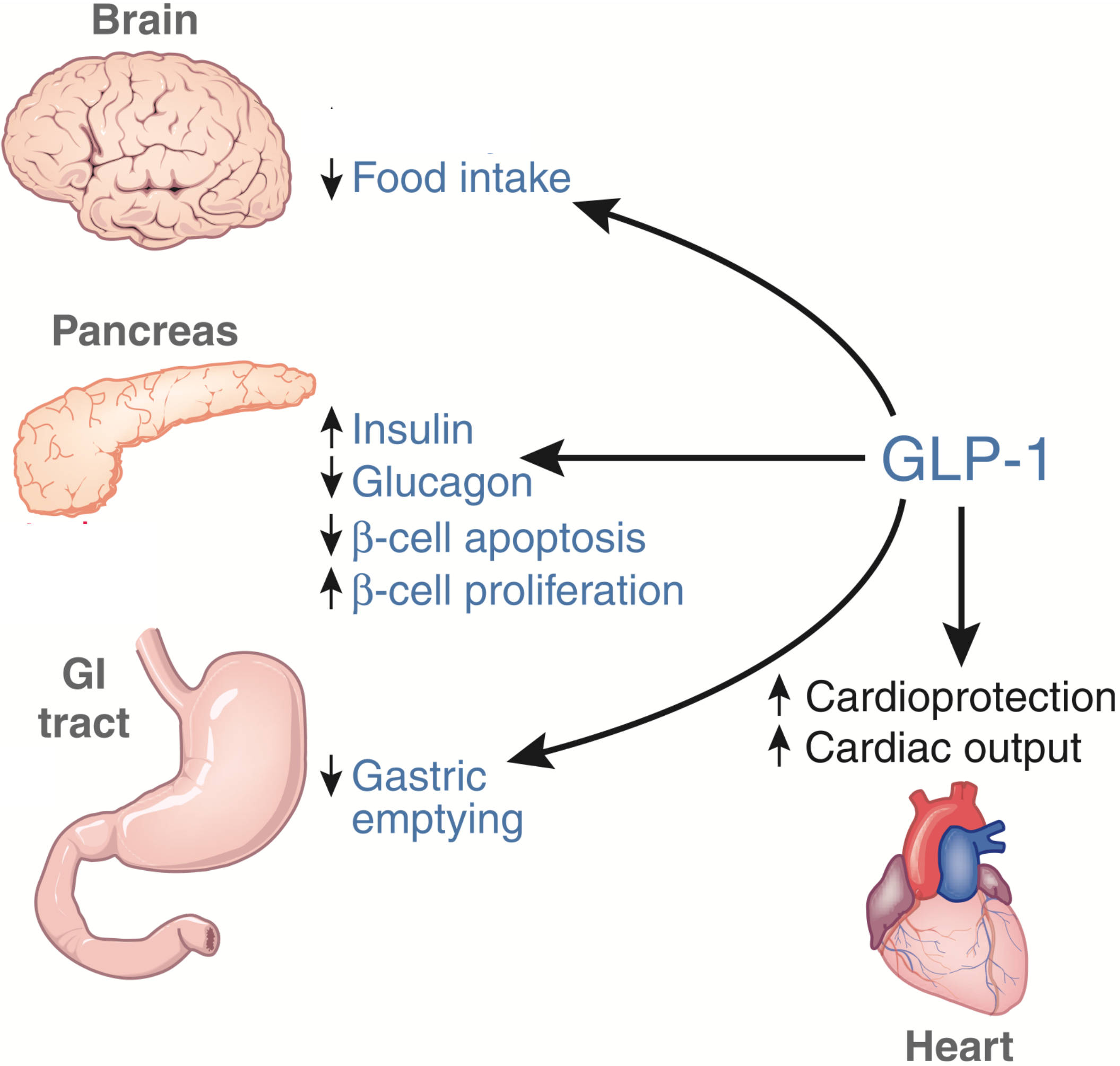
## Glucagon-like Peptide-1

# GLP-1 incretin hormone



Cooke D, et al., *Nat Rev Drug Discovery* 2006; 5: 919-931

# GLP-1



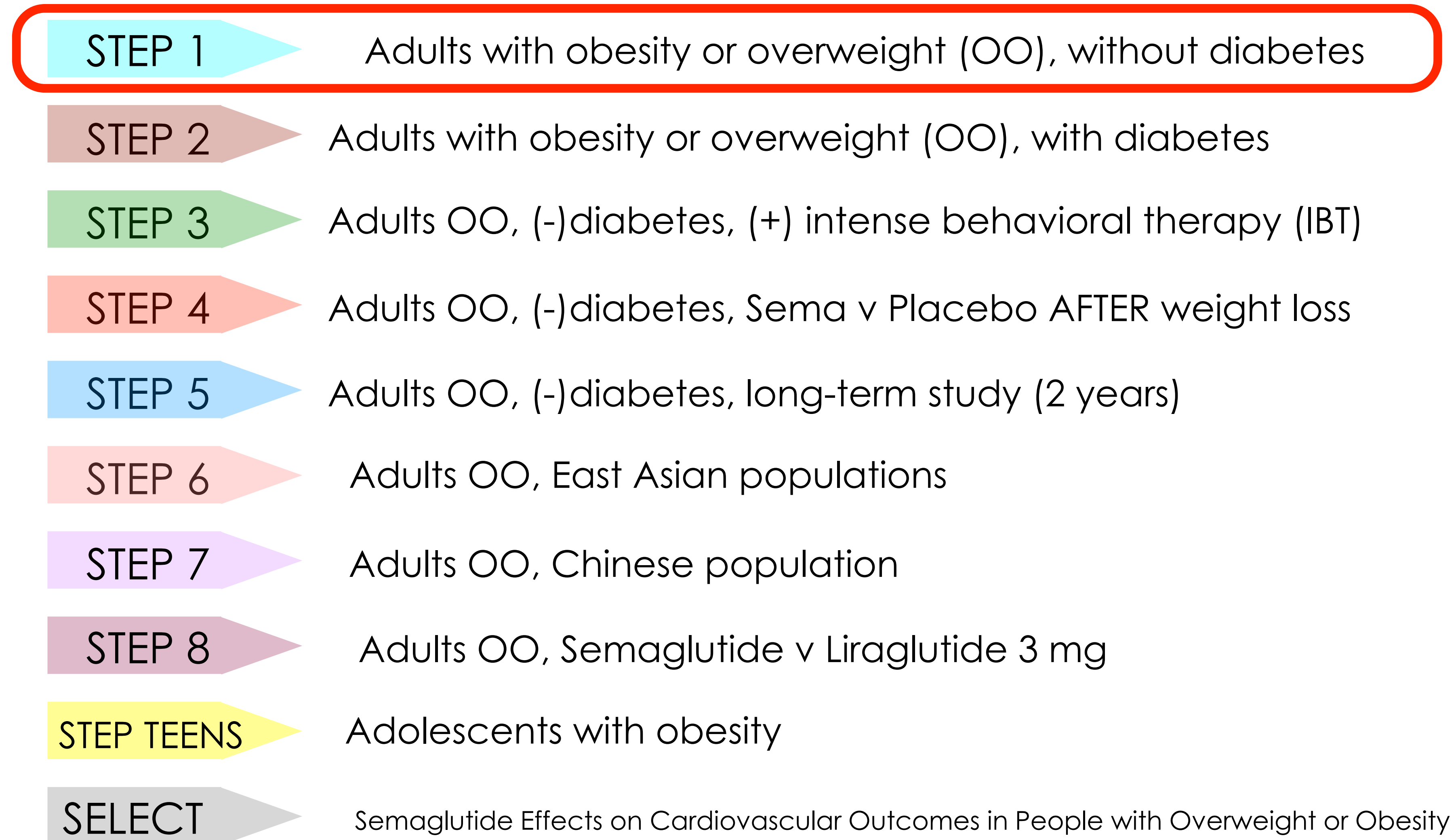
Adapted from Seino Y, et al., *J Diabetes Investig* 2010;1:8-23



# GLP-1 Receptor Agonists

## Semaglutide 2.4 mg (Wegovy<sup>®</sup>)

### Semaglutide Treatment Effect in People with Obesity (STEP) Program



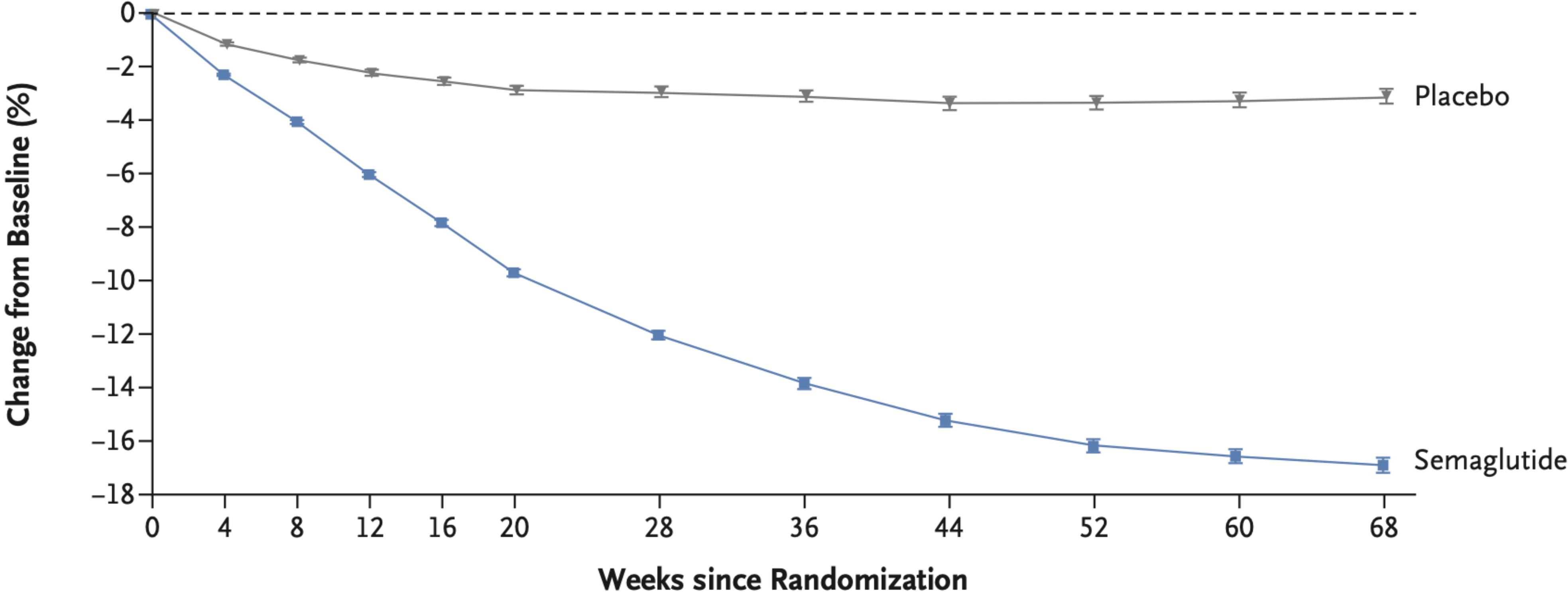
# GLP-1 Receptor Agonists

Semaglutide 2.4 mg

**STEP 1**

n = 1961

**Body Weight Change from Baseline by Week, Observed On-Treatment Data**



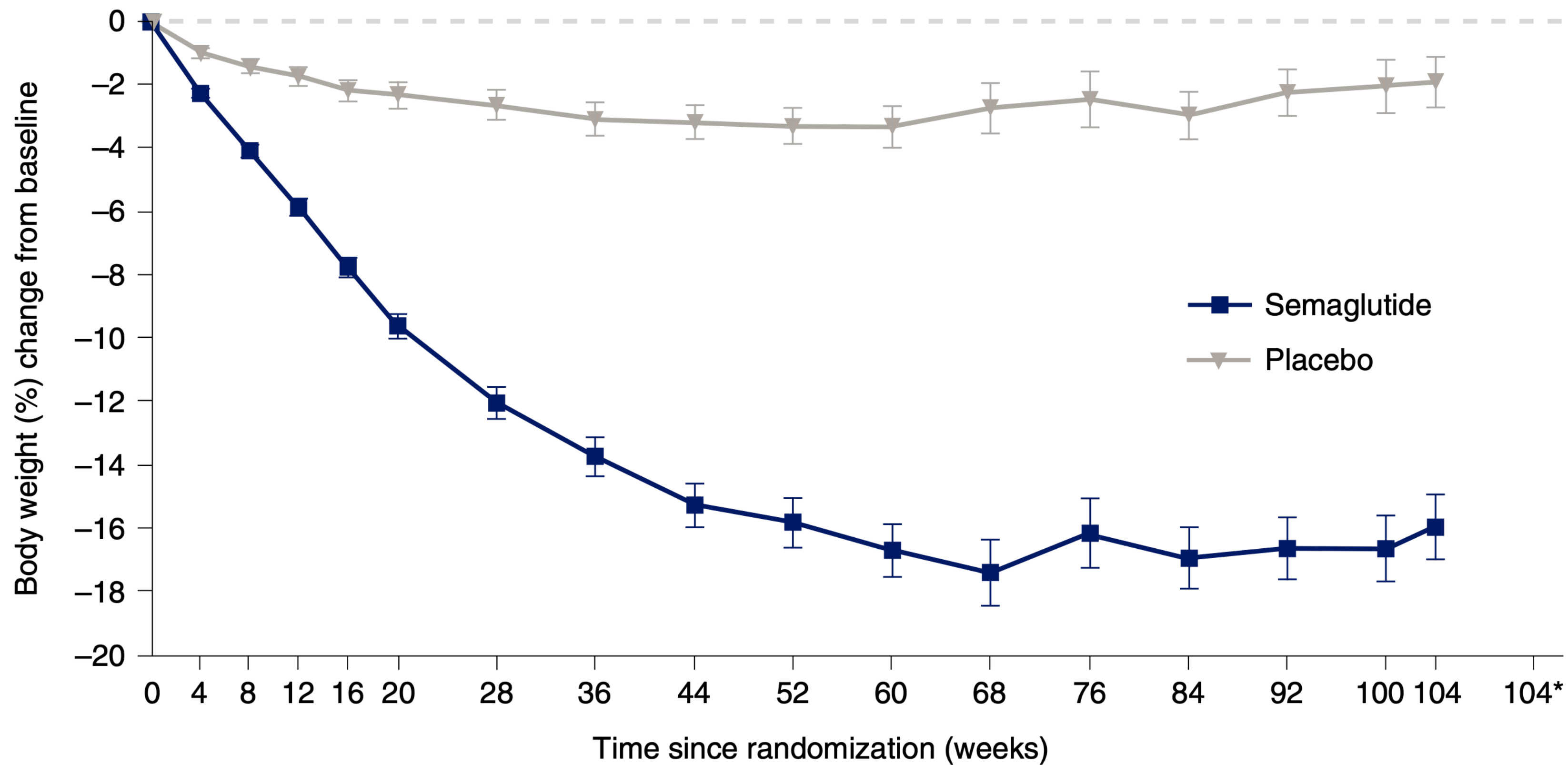
**No. at Risk**

Placebo	655	647	637	613	607	593	576	555	529	520	514	499
Semaglutide	1306	1283	1259	1225	1206	1193	1176	1166	1135	1115	1100	1059

# Semaglutide 2.4 mg

## STEP 5

Semaglutide n=152; Placebo n=152



Number of participants

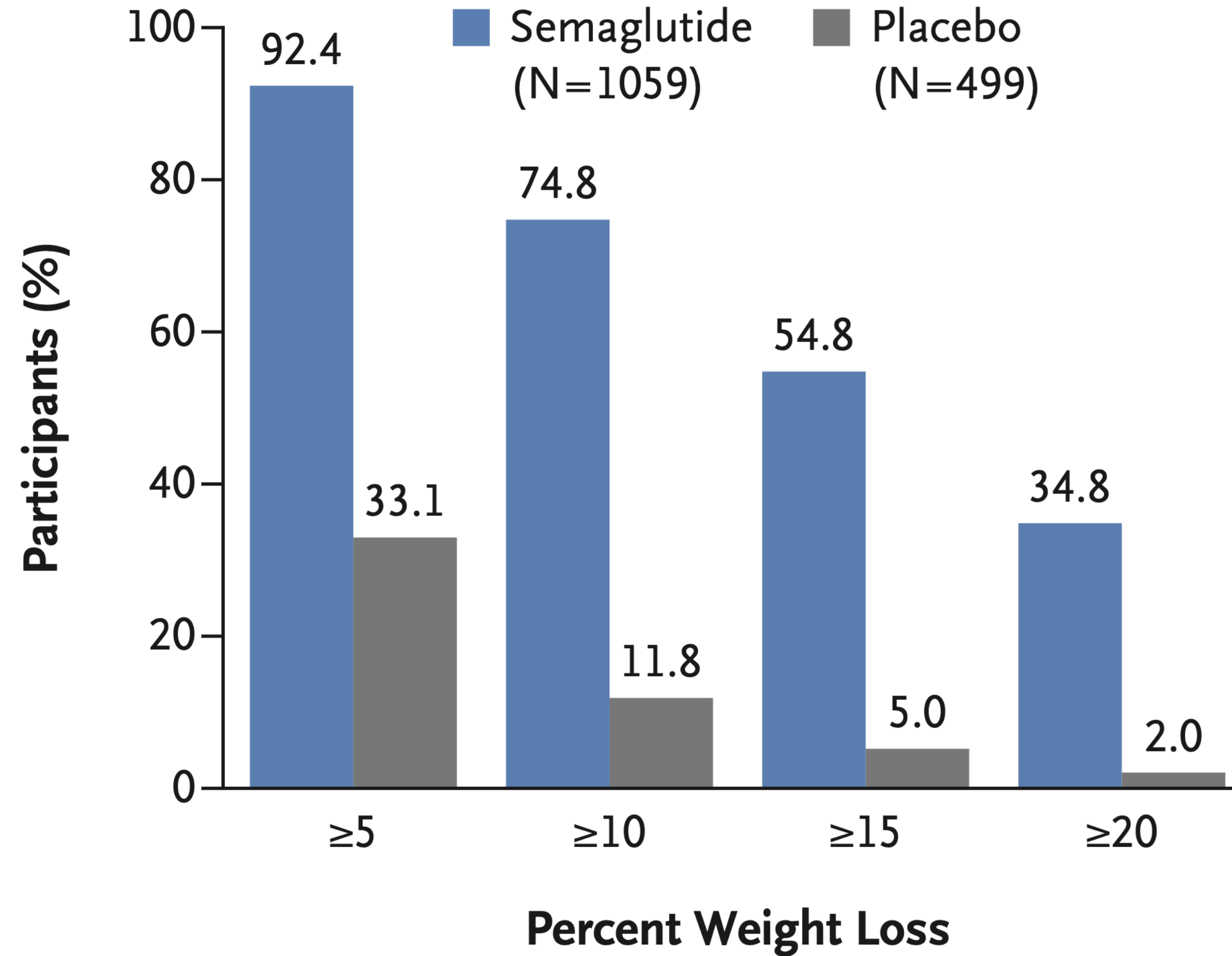
Semaglutide	152	150	151	151	151	152	152	149	146	149	136	101	92	140	137	134	144
Placebo	152	149	146	146	143	141	133	132	131	129	118	89	74	116	117	107	128

# Semaglutide 2.4 mg | categorical weight loss analysis

**STEP 1**

n = 1961

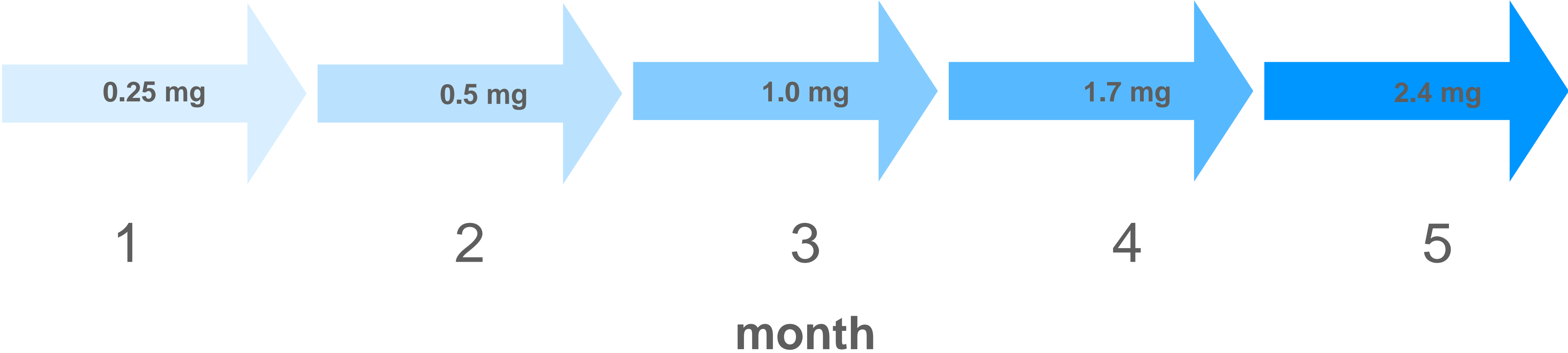
## On-Treatment Data at Wk 68



Discontinuation (AE): 7% v 3.1%

# Semaglutide 2.4 mg (Wegovy)

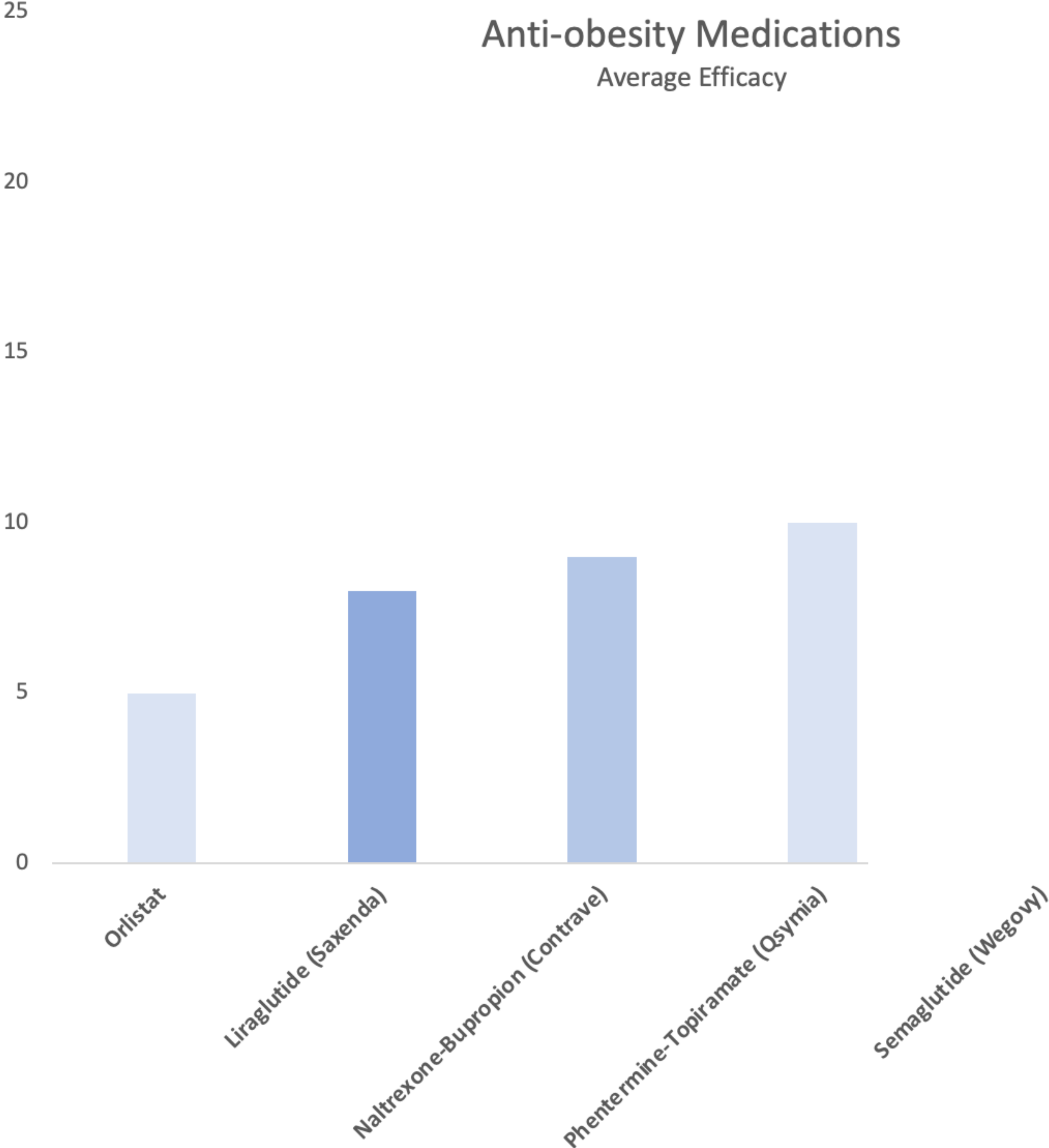
Weekly Subcutaneous Self-injection



# Anti-obesity Medications

Average Efficacy

% weight loss



# Incretin Hormones

## Common side effects

nausea, vomiting, constipation, diarrhea, fatigue

### ➤ Contraindications

- Pregnancy
- Personal or family history of medullary thyroid cancer
- Personal or family history of MEN Type 2
- Use of other GLP-1 enhancing medications

### ➤ Cautions

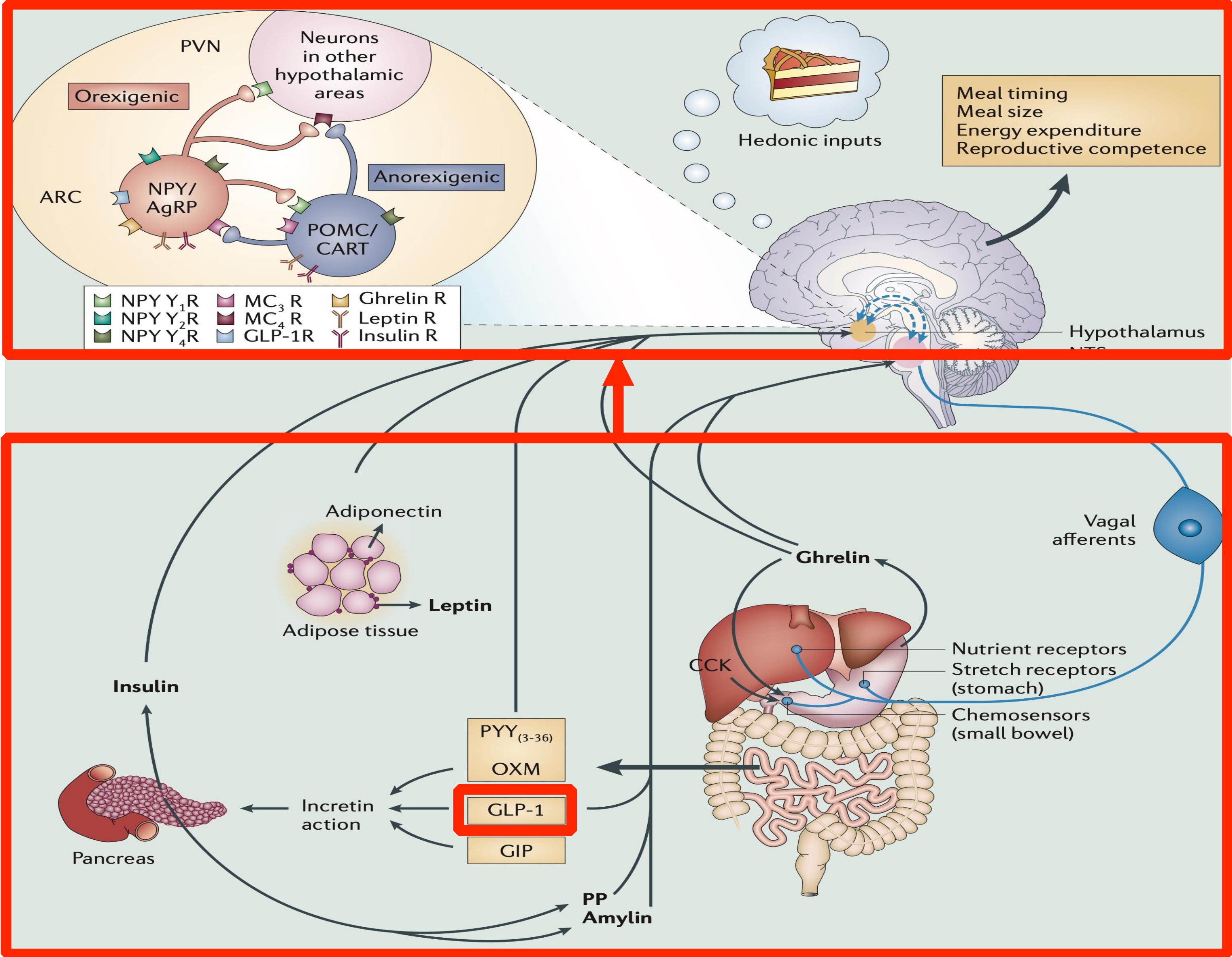
- History or risk factors for pancreatitis
- Gastroparesis
- Hypoglycemia (patients on insulin or sulfonylureas)

The background of the slide is a 3D-rendered tunnel. The walls and floor are a light grey color. The ceiling is composed of a series of white, circular rings or pipes that recede into the distance, creating a strong sense of perspective. The lighting is soft and even, highlighting the metallic texture of the rings.

**What's in the pipelines?**



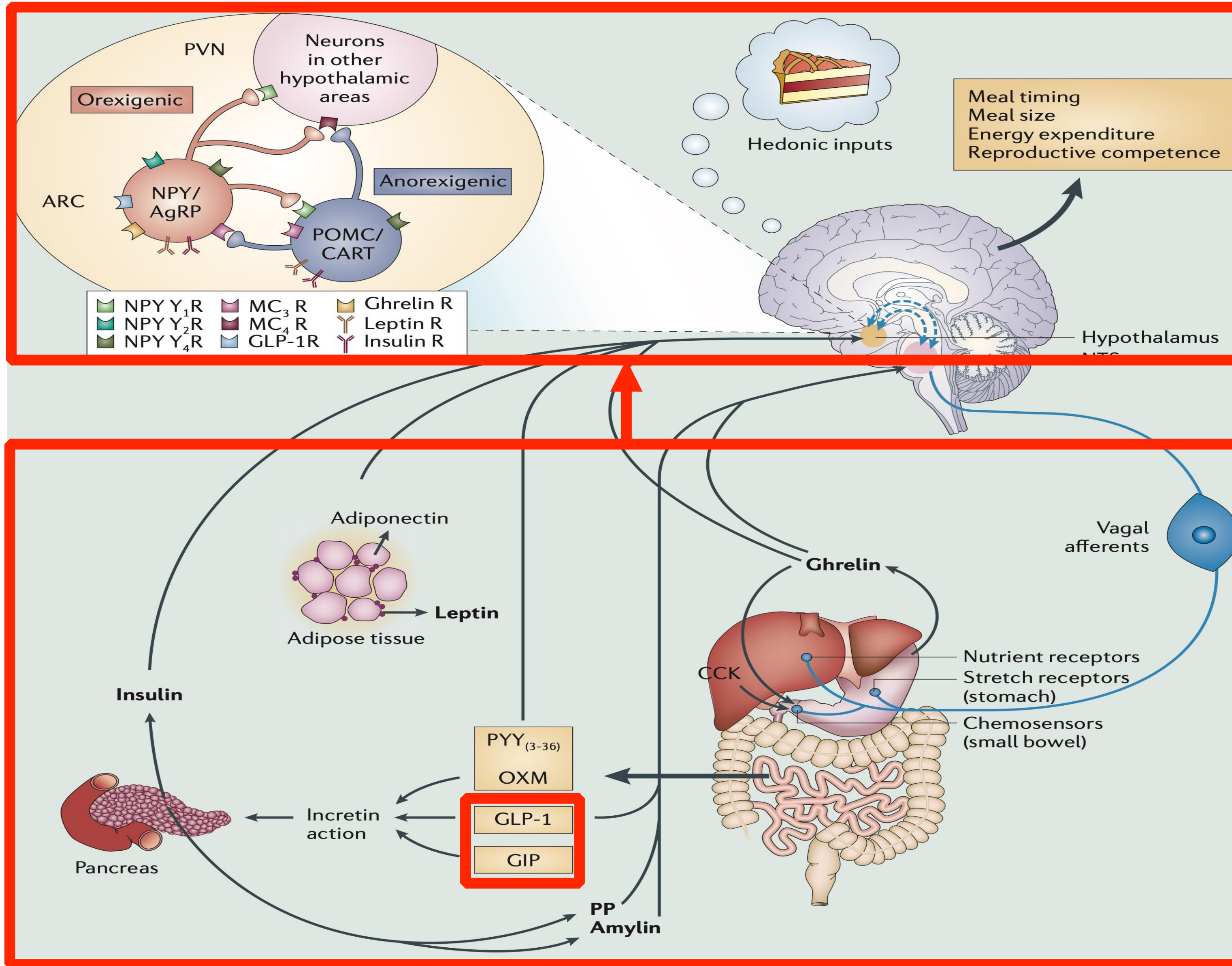
# Biology of weight regulation



Signals

# GLP-1 + GIP (Tirzepatide)

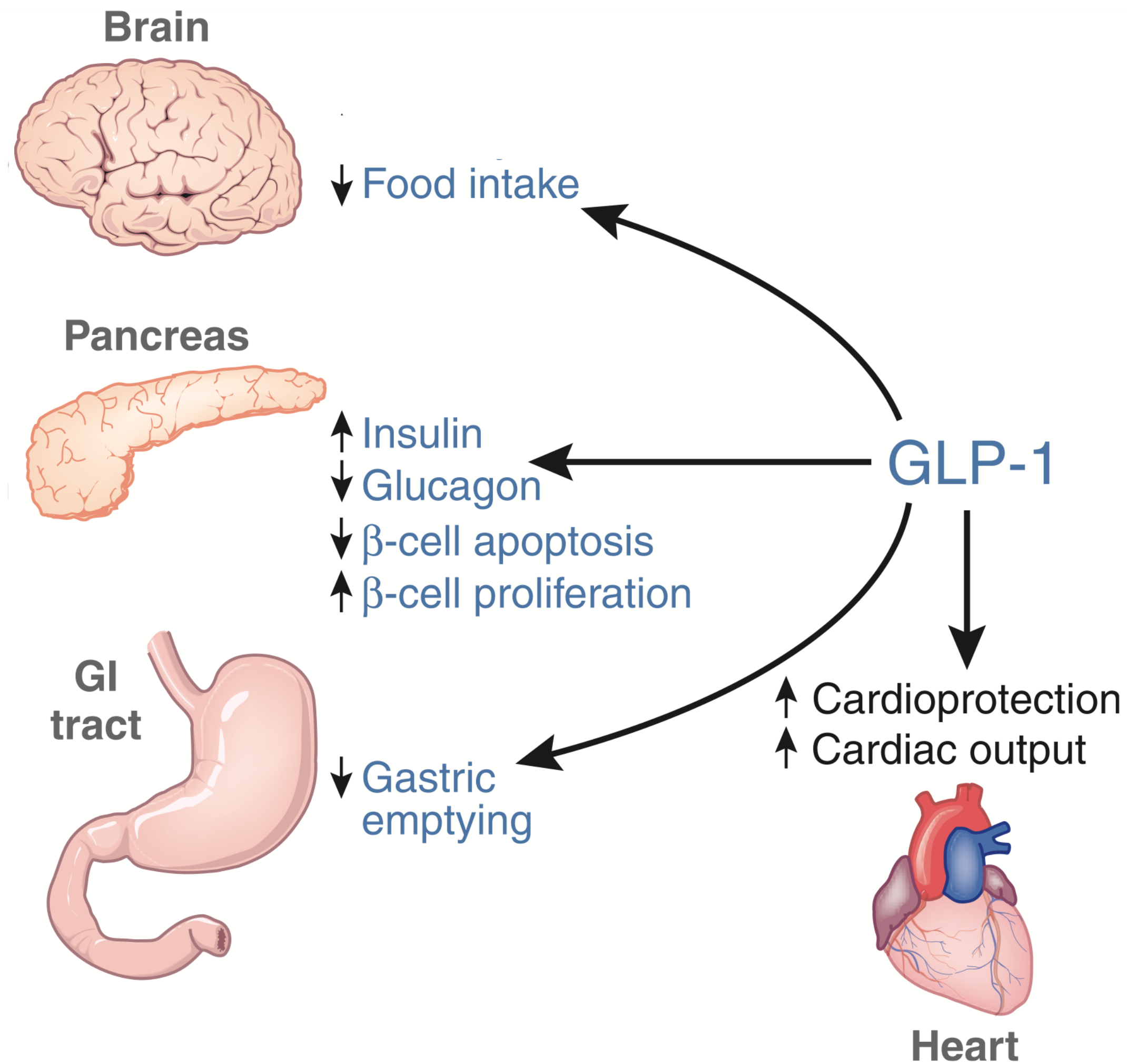
# “Twincretin”



# GIP

glucose-dependent insulinotropic polypeptide

# GIP



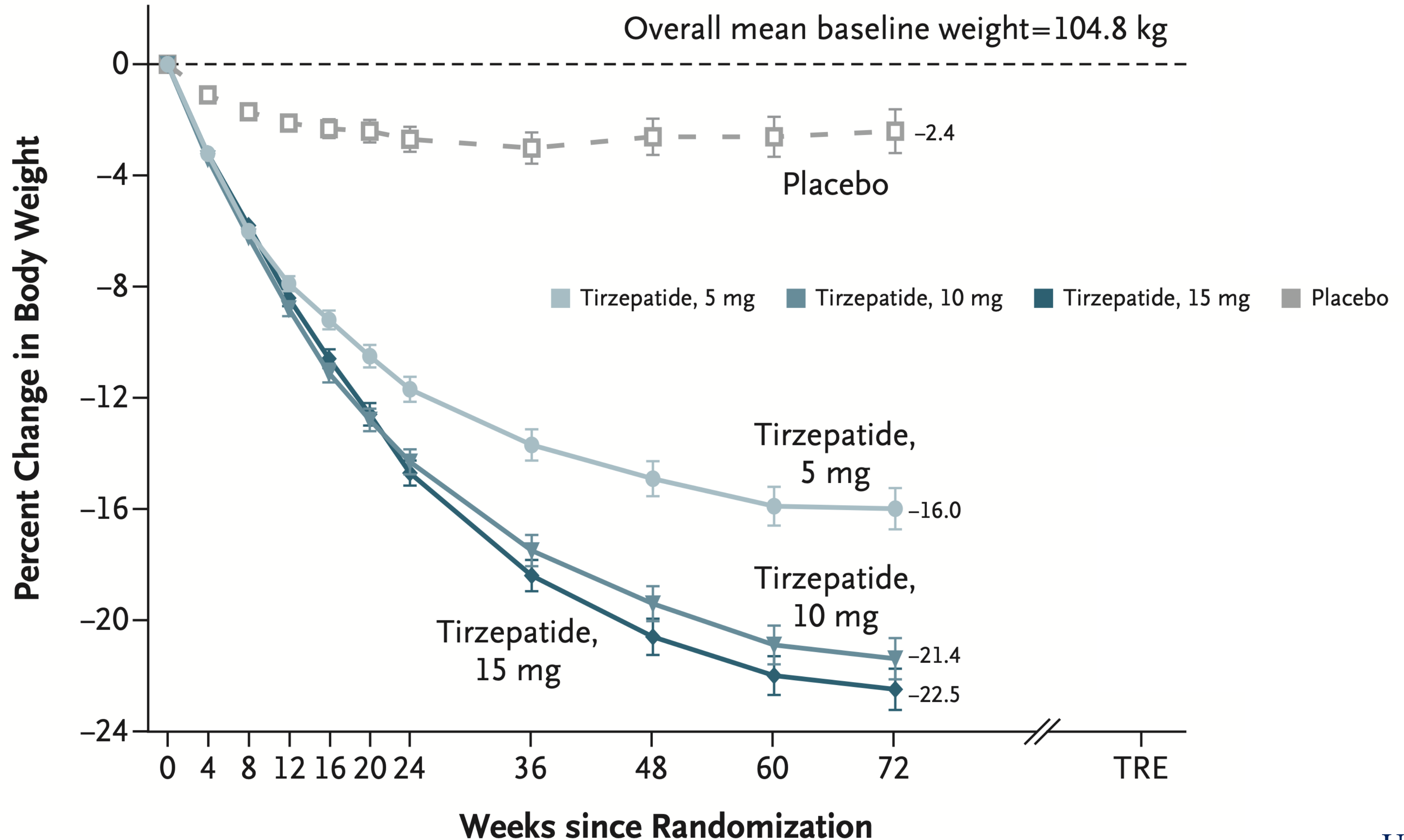
ORIGINAL ARTICLE

# Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D.,  
Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D.,  
Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D.,  
Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D.,  
and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators\*

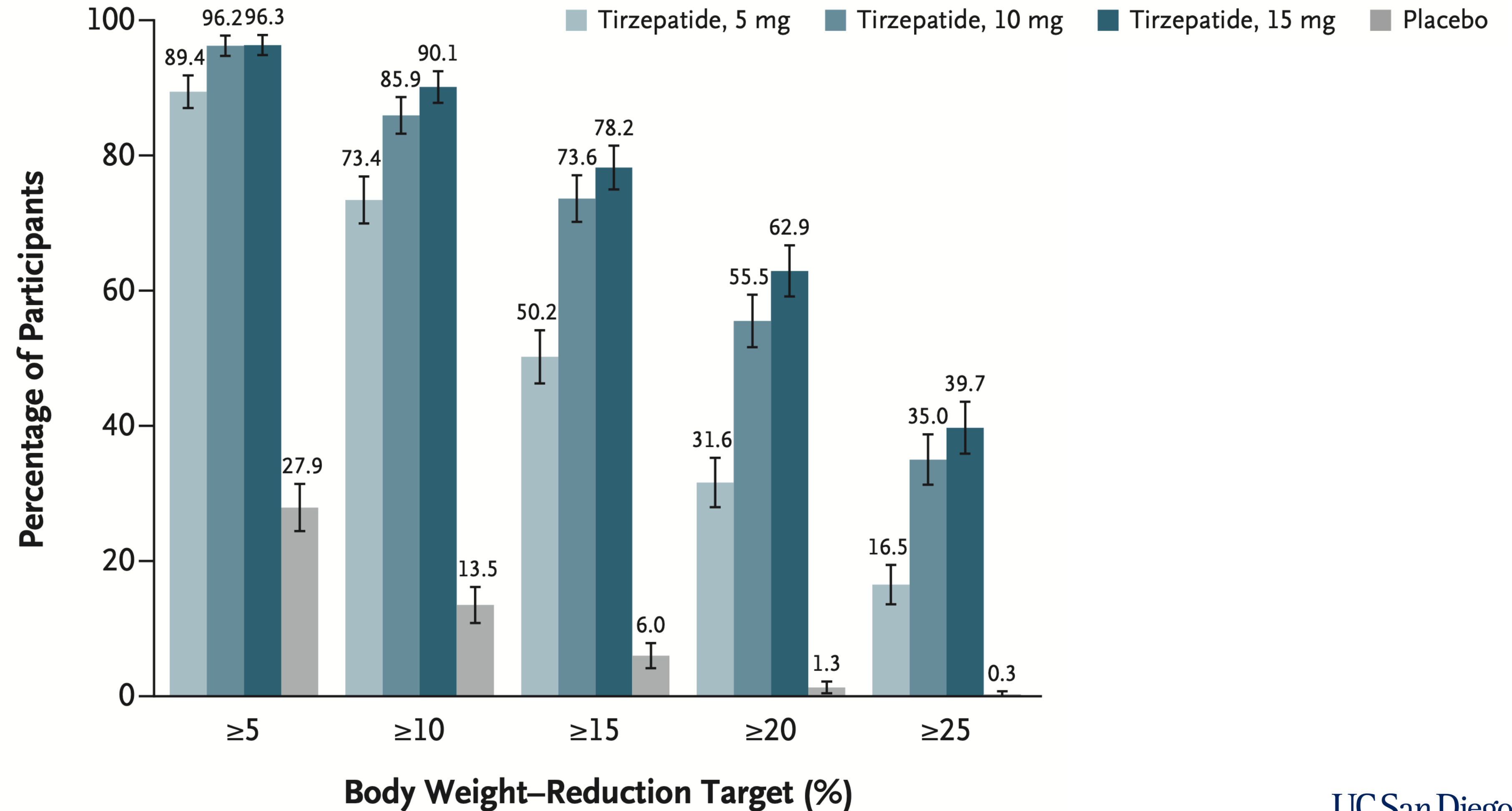
# Tirzepatide | mean weight loss

Percent Change in Body Weight by Week (efficacy estimand)



# Tirzepatide | categorical weight loss analysis

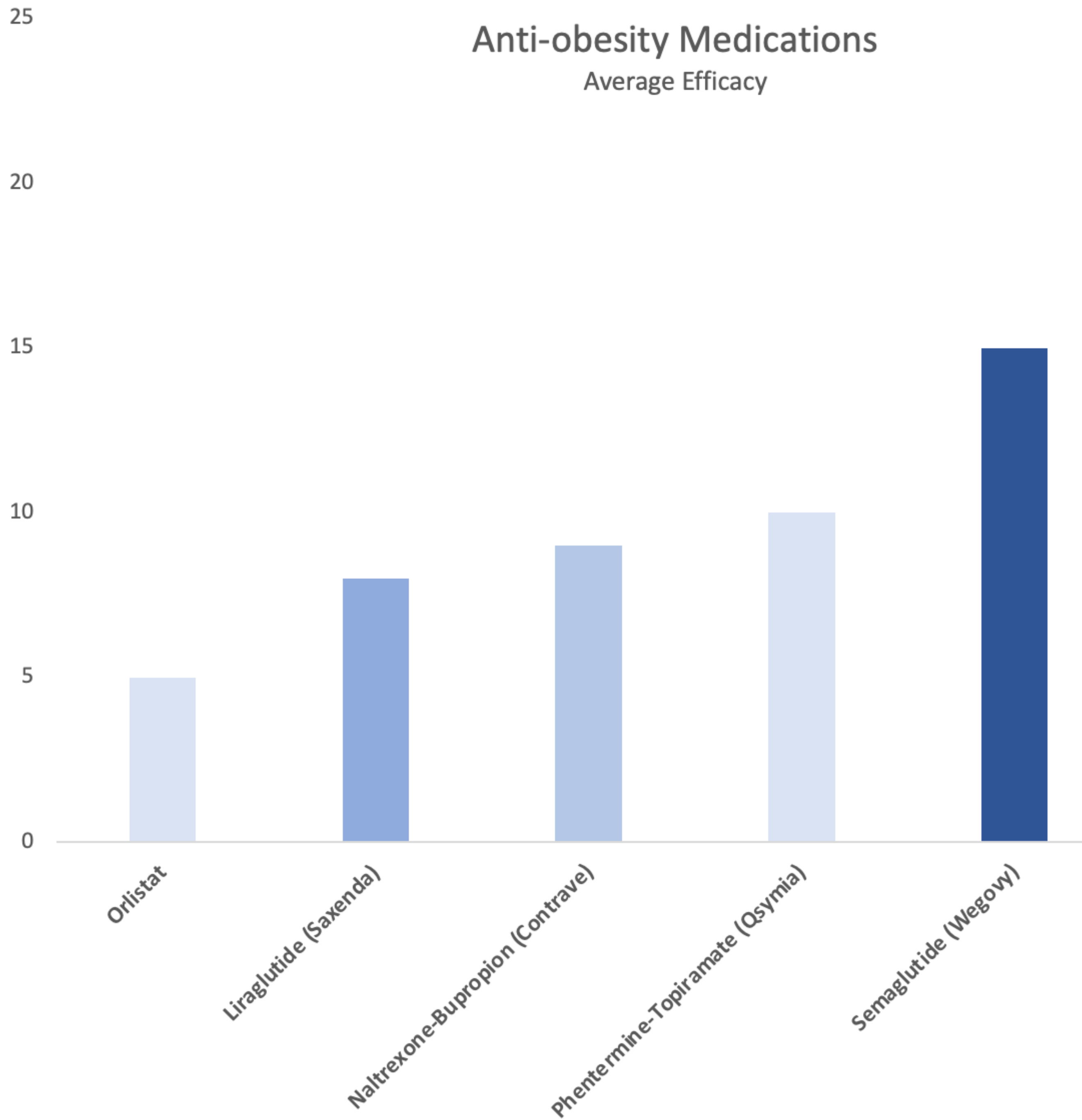
Participants Who Met Weight-Reduction Targets (efficacy estimand)



# Anti-obesity Medications

Average Efficacy

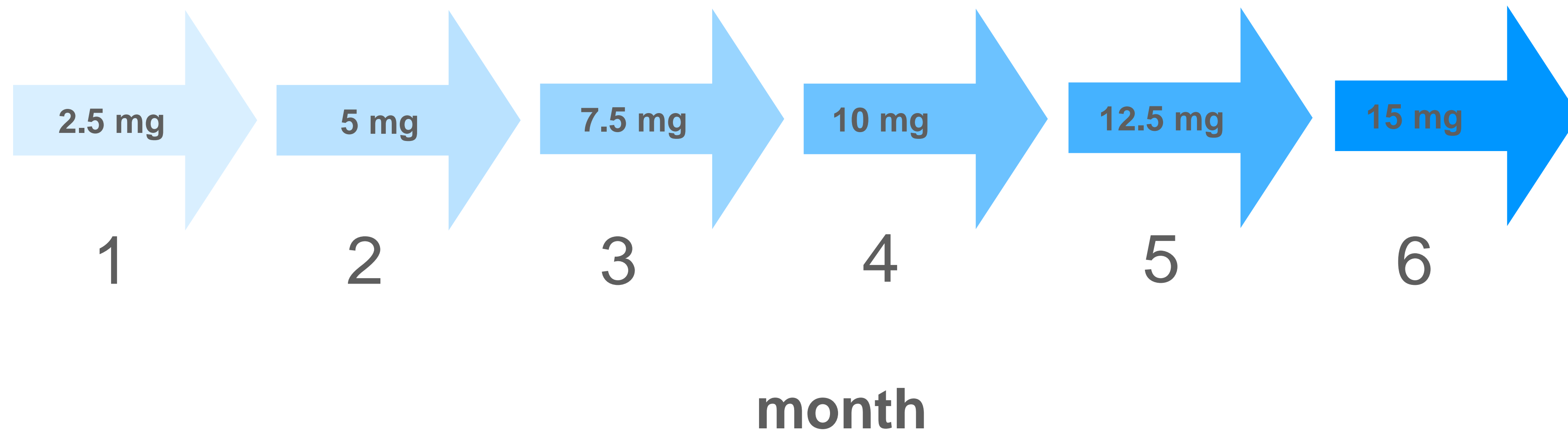
% weight loss



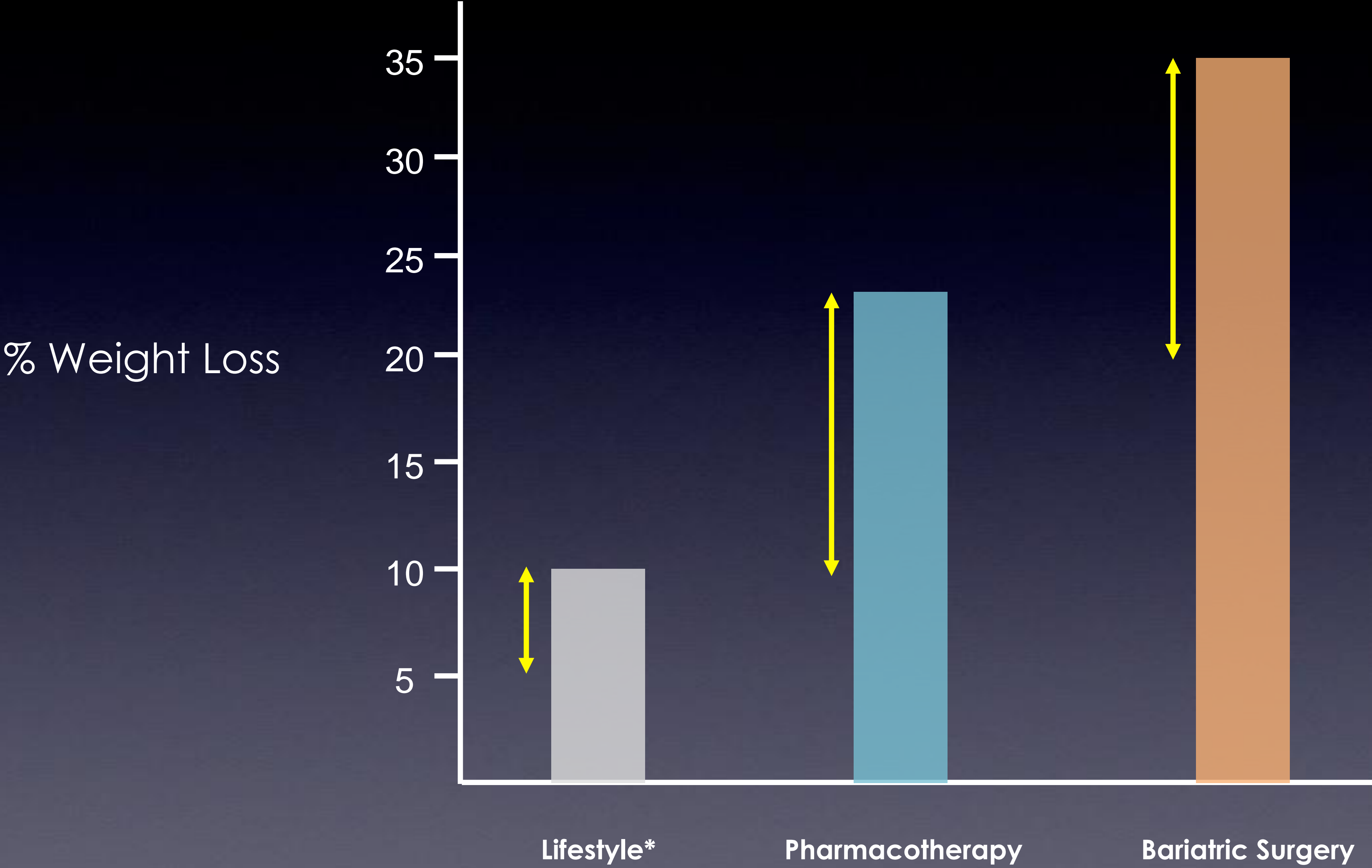


# Tirzepatide (Mounjaro™)

Weekly Subcutaneous Self-injection

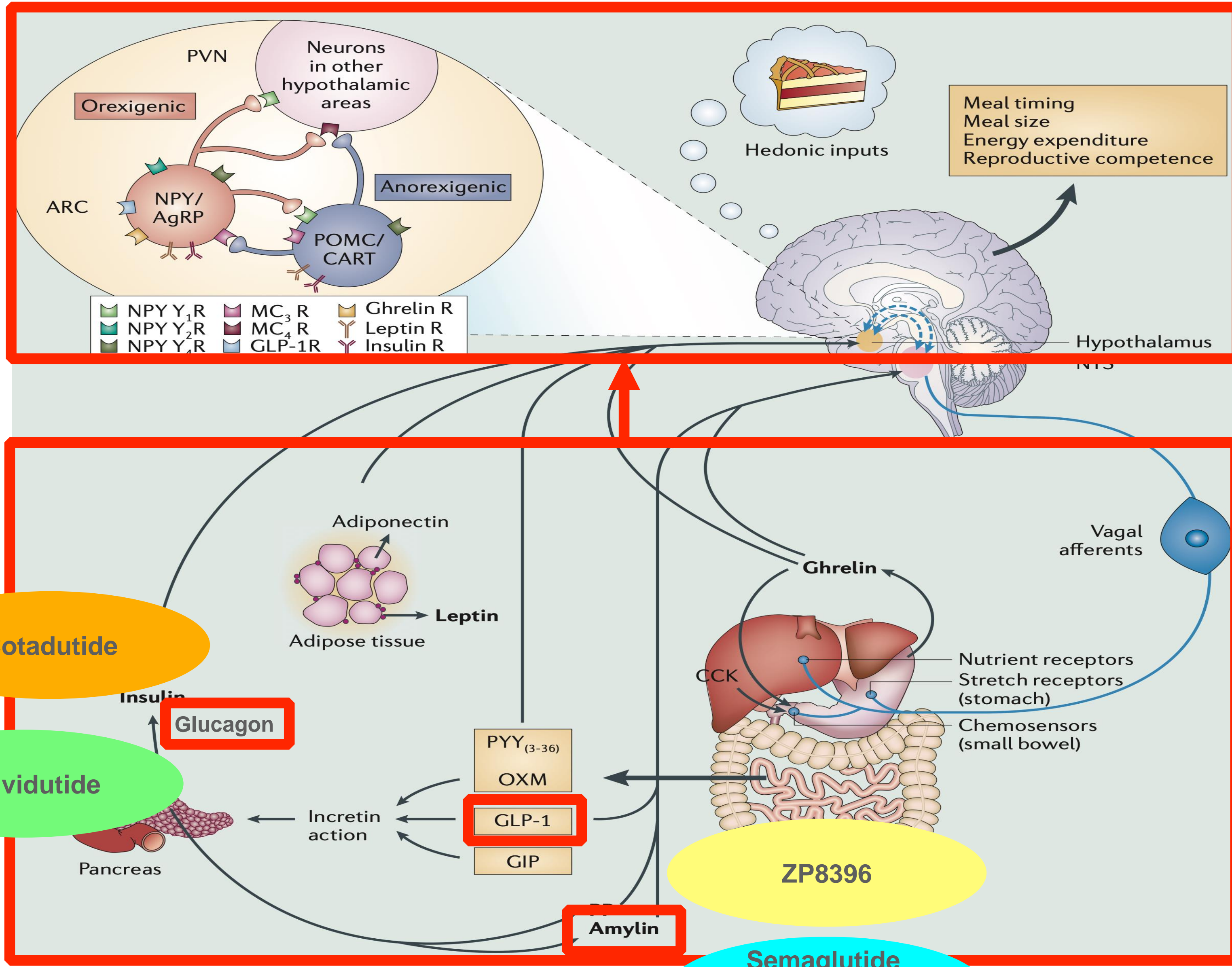


# Expectations Long-term Weight Loss



\*Lifestyle therapy is always employed with pharmacotherapy and/or bariatric surgery

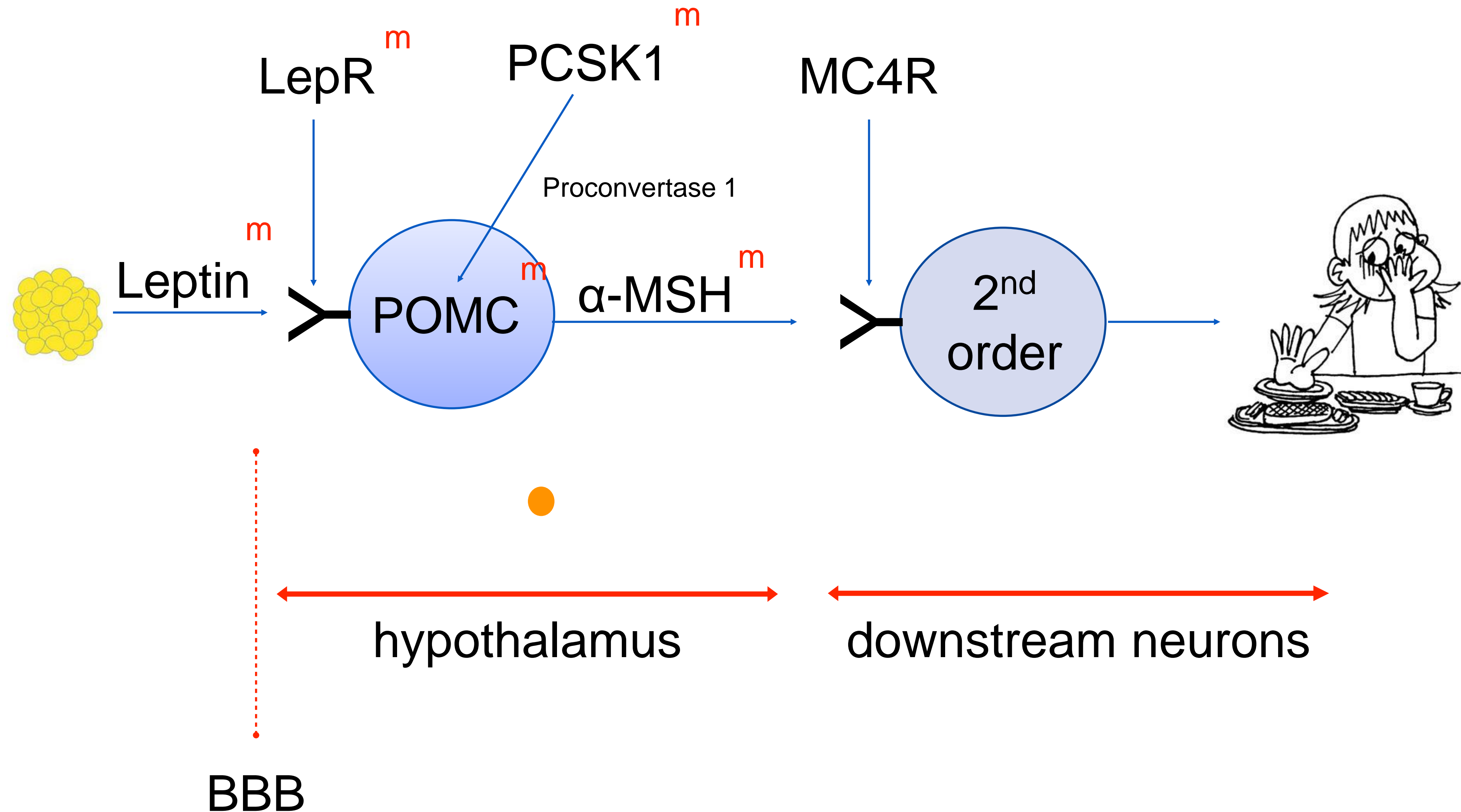
# Biology of weight regulation | pharmacotherapy early development



# Monogenic Obesity

Setmelanotide (Imcivree™)

● Melanocortin 4 Receptor Agonist



# Setmelanotide (Imcivree™)

- ✓ FDA approved for
  - homozygous mutations of LepR, PCSK1, POMC
  - Bardet-Biedl Syndrome
  - pending for hypothalamic obesity
- ✓ Clinical features
  - Early onset obesity (age  $\leq$  10)
  - History of hyperphagia

# Practical tips for prescribing

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1. Medicare: don't bother with insurance coverage
2. Medi-cal: paradoxically, great coverage in California (for now)
3. Use cost savings options -> refer to respective websites
4. Document lifestyle counseling or participation in a program
5. For incretin therapies, document failure of or contraindications to phentermine, phen/top, bupropion/naltrexone, if appropriate (especially tricare)
6. Return no less frequently than every 3 months, document weight loss
7. If possible, train MA to do paperwork, expect prior authorization

# Take Home Messages

1. Obesity is a chronic metabolic disease
2. Consider anti-obesity pharmacotherapy when appropriate
3. In primary care, try treating and refer challenging, refractory, or complex patients
4. Anti-obesity pharmacotherapy is rapidly advancing
5. Some questions remain to be answered regarding long-term therapy, safety, and cost effectiveness